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RESULTS OF SALVAGE CRYOABLATION OF THE PROSTATE AFTER RADIATION: IDENTIFYING PREDICTORS OF TREATMENT FAILURE AND COMPLICATIONS

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ABSTRACT

Purpose: We conduct a critical evaluation of cryoablation of prostate cancer after failure of full dose radiotherapy to identify predictors of treatment failure and complications.

Materials and Methods: A total of 125 cryoablation procedures were performed in 118 patients with proved local recurrence after full dose radiotherapy. Followup includes serial prostate specific antigen (PSA) and biopsy at 6,12 and 24 months. Kaplan-Meier plots were constructed for different PSA cutoffs. We separately analyzed different cohorts based on T stage, Gleason score, PSA before cryoablation and endocrine therapy status.

Results: Of the 118 patients 114 had serum PSA nadir less than 0.5 ng./ml. Median followup was 18.6 months (range 3 to 54). Of the biopsy cores 3.1% (23 of 745) from 7 patients contained persistent viable cancer. Kaplan-Meier plots showed patients free of histological failure leveling at 87% and free from biochemical failure at 68%, 55% and 34%, respectively, with PSA greater than 4, 2 and 0.5 ng./ml. PSA greater than 10 ng./ml. before cryoablation, Gleason score 8 or greater before radiation and stage T3/T4 disease appeared to predict an unfavorable biochemical outcome. Serious complications included 4 rectourethral fistulas (3.3%) and severe incontinence (6.7%). Strong predictors of complications included bulky disease for fistulas and prior transurethral surgery.

Conclusions: Salvage cryoablation after radiation can achieve reasonable biochemical and histological results with acceptable morbidity. Cryoablation appears to be a reasonable treatment option for this patient population with few viable therapeutic options, provided vigorous patient selection criteria are adhered to.

KEY WORDS: salvage therapy, cryosurgery, prostate, radiation

Despite recent advances in treatment of clinically organ confined prostate cancer, local treatment failure remains problematic for some patients.[1,2] As published in radiation oncology literature, local recurrences develop in 75% of patients with positive biopsy in 10 years.[3] Untreated local recurrence will usually and eventually result in the development of distant metastasis and ultimately death, with a median survival of only 33 months.[4] Options for salvage therapy with curative intent are somewhat limited and include salvage prostatectomy, salvage cystoprostatectomy, cryoablation and limited experience with salvage brachytherapy.[5–8] Since 1994 we have been performing salvage cryoablation in select patients with clinically localized failure after radiation of prostate cancer. We critically evaluate our results and address the question of whether there is a role for cryoablation as a salvage modality for prostate cancer and if so, to identify the optimal candidates as well as predictive factors of treatment failure and complications.

MATERIALS AND METHODS

From December 1994 to September 1999, 125 cryoablation procedures were performed in 118 patients, including 7 who underwent repeat procedure. Median age was 68 years. All patients had increasing serum prostate specific antigen (PSA) on 3 consecutive determinations at least 2 years after administration of radical radiation therapy with curative intent, including external beam radiation in 113 and interstitial seed implantation in 5. All patients except 3, who had negative biopsy but clinical local recurrence and no evidence of distant disease, had biopsy proved local recurrence. There were 10 patients who had undergone prostatic transrectal resection. The significant likelihood of urinary incontinence was emphasized to them. All patients were classified as acceptable anesthetic risks, and all had negative pelvic and abdominal computerized tomography as well as radionuclide bone scan. Serum PSA was less than 20 ng./ml. in all patients except 4, who either had negative pelvic lymphadenectomy or negative computerized tomography guided aspiration biopsy of pelvic nodes (table 1). Of the 118 patients 71 had been on hormone therapy before cryoablation. All patients on endocrine therapy immediately discontinued it postoperatively.

Cryoablation. The CRYOcare‡ system was used in all cases except for the initial 11 in which a Candela§ system was used. Preoperative, intraoperative and postoperative transrectal ultrasound assessment was performed with the Aloka¶ ultrasound transducer. An in-house software package provided 3 dimensional ultrasound images for guidance of probe placement.[9,10] A urethral warming device‖ was used in all

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§Candela, Wayland, Massachusetts.
‖Cook Urological, Spencer, Illinois.
¶Aloka Co. Ltd., Wallingford, Connecticut.

TABLE 1. *Tumor characteristics of the 118 patients undergoing salvage cryoablation*

Clinical tumor stage:	No. Pts.	
	Initial Presentation Before Radiation	After Radiation Before Cryoablation
T1	13	0
T2	95	48
T3	10	66
T4	0	4
Totals	118	118
Gleason grade:		
2–4	13	2
5–7	88	65
8–10	17	48
Totals	118	115*
Serum PSA (ng./ml.):		
Less than 5	0	60
5–10	55	40
Greater than 10	63	18
Totals	118	118

* Three patients had negative biopsy after radiation but had clinical evidence of local disease recurrence.

cases. There were 5 to 6 cryoprobes for application, depending on prostate size and configuration. Three thermocouples were inserted into the periprostatic area (left side, right side and midline near the apex). There were 2 freeze thaw cycles in all cases, occasionally "pulling back" the probes in the caudal direction before the second freeze, taking into account the configuration, prostate size and location of recurrent tumor. Postoperative drainage was performed with a urethral Foley catheter for 24 hours, and a trocar type suprapubic cystostomy catheter was left in for 2 weeks. Transrectal ultrasound assessment with color flow Doppler imaging was performed on postoperative day 1. Serial PSA levels were done at 3, 6, 12, 24 and 36 months postoperatively. Transrectal ultrasound guided biopsy was performed (D. B. D.) at the same time wherever logistically feasible.

Because we are at the only Canadian center offering salvage cryoablation of prostate cancer, many patients had to travel a distance for followup. Despite this inconvenience, there was an 83% overall compliance with followup biopsy attendance at our center. A comparable followup regime was conducted, if at all feasible, on the remaining patients who were followed by referring physicians, and data were obtained. In the more recent patients the 3-month biopsy was omitted if PSA was less than 0.5 ng./ml. and they were clinically well. There were 4 quadrant biopsies routinely done with additional lesional directed biopsies as indicated.

Statistical analysis. Actuarial survival curves were calculated for overall and metastatic-free survival with Kaplan-Meier limit estimates, and tests of significance were based on the log-rank tabulations. Actuarial survival curves were computed with commercially available software. Followup ranged from 3 to 54 months (median 18.6). To our knowledge there is no standard definition of biochemical failure after salvage cryoablation, so we elected to construct Kaplan-Meier plots with a failure definition of PSA greater than 4, 2 and 0.5 ng./ml. A Kaplan-Meier survival curve was also constructed for patients free of local recurrence based on rebiopsy.

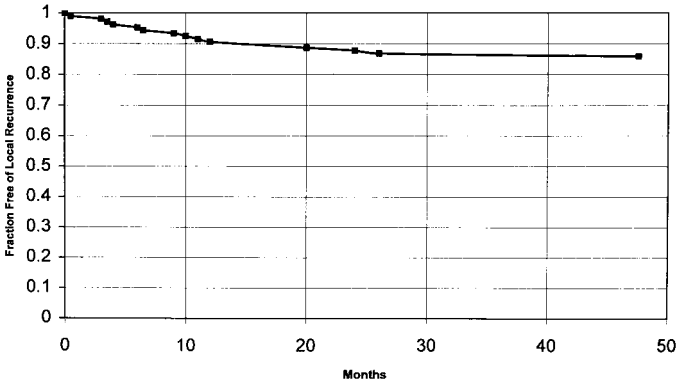

FIG. 1. Kaplan-Meier survival curve for local recurrence of prostate carcinoma after salvage cryoablation.

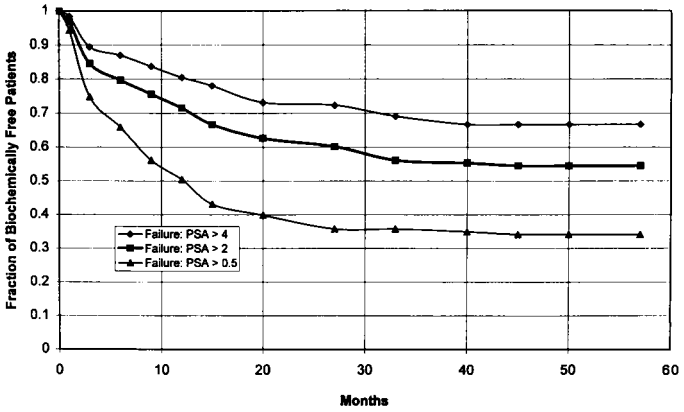

FIG. 2. Kaplan-Meier survival curves for biochemically-free cases followed after salvage cryoablation of prostate. Failure defined as PSA greater than 4, 2 and 0.5 ng./ml.

RESULTS

On biopsy followup 3.1% (23 of 745) of the cores were positive. These were obtained from 7 patients in the total salvage cryoablation population. All 7 patients underwent second cryoablation. Of the 118 patients 114 (96.6%) had PSA nadir less than 0.5 ng./ml., the overwhelming majority of which was attained at the first 3-month followup. The Kaplan-Meier plot showed patients free of proved histological local recurrence (fig. 1). Positive biopsies were seen mostly in the first year. One patient had several negative biopsies but at 48 months, he had 1 positive biopsy core when there was a progressive increase in PSA. Figure 2 depicts patients who were "biochemically free of failure," with a PSA of 4, 2 and 0.5 ng./ml. All curves tended to level off after 30 months.

With the various biochemical failure definitions of PSA greater than 4, 2 and 0.5 ng./ml., approximately 68%, 55% and 34% of patients, respectively, were free of biochemical failure. There were 10 patients, including 9 with PSA greater

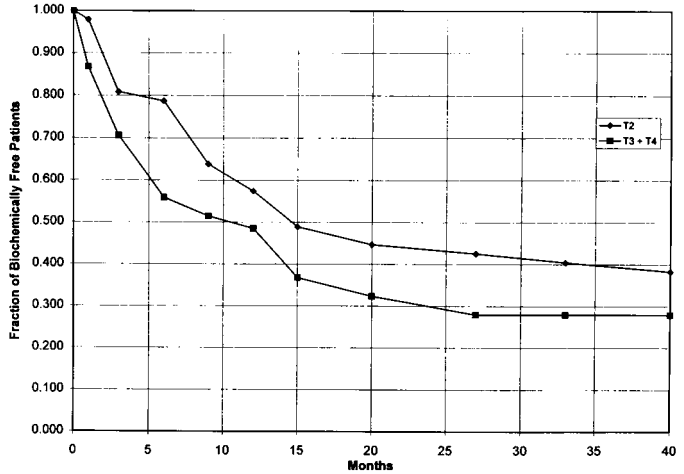

FIG. 3. Kaplan-Meier survival curves for patients with stages T2 versus T3 and T4 before cryoablation. Failure defined as PSA greater than 0.5 ng./ml.

TABLE 2. *Prevalence of viable tissue on followup biopsy at various postoperative intervals*

	% Cores	% Pts.
Residual viable glands (mos.):		
3	21.5	41.5
6	16.0	34.2
12	23.4	40.0
24	42.0	50.0
Residual viable stroma (mos.):		
3	5.8	11.3
6	7.7	7.9
24	32.0	24.0
122	17.1	12.0

than 5.0 ng./ml. and 1 with less than 5.0 ng./ml., in whom clinically evident distant metastatic disease (bones, liver, pelvic nodes) had subsequently developed. In addition to the aforementioned positive biopsy results, serial biopsy revealed residual viable glandular and stromal elements in a significant proportion of biopsies at various intervals (table 2). Other less clinically relevant "early" histopathological findings included fibrosis, hemorrhage, necrosis, hemosiderin deposits, vascular infarction and inflammatory cell infiltrates. Subsequent biopsies revealed calcification periductal hyalinization and squamous metaplasia.

Cryoablation complications. Local complications relating to salvage cryoablation are listed in table 3. Four rectourethral fistulas were diagnosed at 4, 4, 6 and 33 months after cryoablation, respectively. All 4 patients had extensive local disease. Biopsy of the fistulous tract via sigmoidoscopy was positive for prostatic adenocarcinoma in 1 of the 4 patients. A fistulous tract between the bladder base and urethra beyond the external sphincter through prostatic parenchyma developed in 1 patient, rendering him totally incontinent. Evidently, this development was due to the persistence of one of the cryoprobe tracts. The remaining fistulas were likely due to the overzealous freezing of bulky tumors. To identify predictive factors for cryoablation failure, tumor characteristics before cryoablation were correlated with postoperative PSA at last followup. Separate Kaplan-Meier plots were constructed for various T stages, Gleason grades, PSA before cryoablation and endocrine therapy status. Separate analyses with PSA greater than 4 and 0.5 ng./ml. were conducted. For the sake of brevity, only plots with PSA greater than 0.5 ng./ml. are shown in figures 3, 4 and 5. The curve with PSA 4 ng./ml. had a significantly higher nadir but showed a similar pattern as the plots with 0.5 ng./ml. Of the 118 patients 71 had been on hormone therapy before cryoablation.

T stage. Because there were only 4 patients with stage T4 disease, we grouped the stage T3 and T4 tumors together on 1 plot and compared them with stage T2 tumors. There was a significant difference in outcome between the 2 groups, with stage T2 tumors doing better ($p < 0.1$, fig. 3).

Gleason score. Because radiotherapy had been known to alter the histological appearance and can alter subsequent Gleason grading, we analyzed 2 groups separately based on patient Gleason scores 2 to 7 and 8 to 10 before radiotherapy. Statistical significance was calculated at $p < 0.1$ (fig. 4).

Serum PSA. Serum PSA before cryoablation was arbitrarily divided into 3 groups, including less than 5, 5 to 10 and greater than 10 ng./ml. Kaplan-Meier plots indicated those cases with PSA greater than 10 ng./ml. before cryoablation did the worst ($p < 0.05$, fig. 5).

Positive cores before cryoablation. The number of positive cores divided into 1 to 3, 4 to 6 and greater than 6 did not appear to have any significant impact on the biochemical results. Therefore, no Kaplan-Meier method was performed based on this parameter.

Prostate volume versus postoperative results before cryoablation. Because a large number of patients was on neoadjuvant hormone therapy, intended to downsize the prostate, the results were not reliable or meaningful. We did categorize the preoperative prostate volume into less than 30, 30 to 50 and greater than 50 cc. There was no statistical difference with the biochemical results except anecdotally. Some glands greater than 40 cc had higher postoperative PSA, which indicated inadequate freezing.

Endocrine response. Of the 118 patients 71 were on endocrine therapy before cryoablation. In a separate analysis of patients who did not receive hormone therapy, with preoperative PSA less than 5, 5 to 10 ng./ml., and greater than 10 ng./ml., which was indicated more clearly, was a poor prognostic factor (fig. 6, *A*). The issue of hormone therapy confused the issue of PSA as a prognostic parameter, as shown by the comparison of the 2 cohorts, including the one that was on hormone therapy and the one that was not (fig. 6, *B*), and showed no prognostic difference. However, of the 18 patients with increased PSA while on hormone therapy clear biochemical failure was demonstrated in 11.

TABLE 3. *Local complications of cryoablation*

Complication	No. Pts. (%)
Rectourethral fistula	4 (3.3)
Vesicourethral fistula beyond external sphincter	1 (0.8)
Incontinence:	
Mild/moderate	16 (66.6)
Severe	8 (33.3)
Outlet obstruction	10 (8.5)
Debris sloughing	6 (5.1)
Bladder neck contracture	2 (1.6)

DISCUSSION

Initial enthusiasm for cryoablation as curative treatment of localized prostate cancer waned after some reports of poor results and unacceptable complications.[11, 12] However, several groups have continued their work on cryoablation with acceptable results in the primary treatment setting,[13–15] whereas others have concentrated on a group of patients in whom primary radiotherapy has failed.[9, 16, 17] Salvage cryoablation has been reported to be more technically challenging than primary cryotherapy, and the complications are more significant. Pisters et al have reported acceptable complications with salvage cryoablation.[16] To our knowledge rectourethral fistulas are the most serious adverse effect of cryoablation, and in 118 our patients there were 4. There was a 4 to 6-month delayed onset in 3 of the patients and, most surprisingly, 33 months for 1, suggesting that tumor invasion is a significant contributing factor. All 4 patients had locally advanced disease (stage T3B and T4A). These cases were deemed marginal earlier in our experience, although we were under pressure to proceed. There was a clear message that patients with bulky disease are poor candidates for salvage cryoablation because of the increased risk of fistula formation, as well as other potential complications, such as injury to the bladder base, ureteral orifices and external urinary sphincter.

We used our own, albeit nonvalidated, questionnaire for urinary, bowel and sexual function, which was administered at each followup visit. Incontinence in this patient directed questionnaire was defined as "urinary leakage which the patient feels some form of protective urinary pad is necessary, either periodically or constantly." In terms of urinary function 20% of the patients had some form of incontinence by our definition and of those 24, 8 had total or near total incontinence. We recognize that a more detailed, validated self-administered questionnaire would most likely yield a higher incontinence rate. Nevertheless, having identified those patients with severe incontinence, we noted that the majority of these 8 had undergone transurethral resection and 2 had undergone repeat cryoablation. We were obviously aware of this prospect in those patients who had undergone

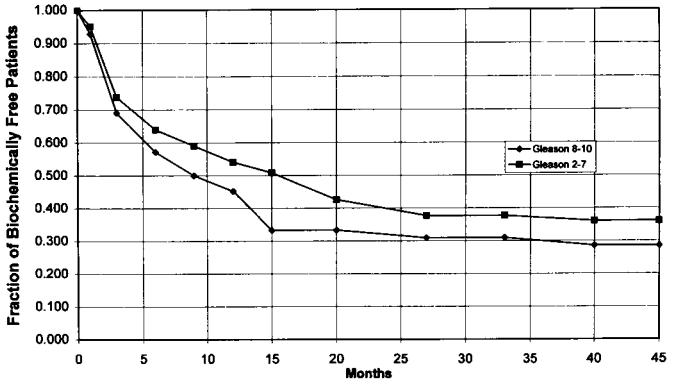

FIG. 4. Kaplan-Meier survival curves for patients with Gleason scores 2 to 7 and 8 to 10 before radiotherapy. Failure defined as PSA greater than 0.5 ng./ml.

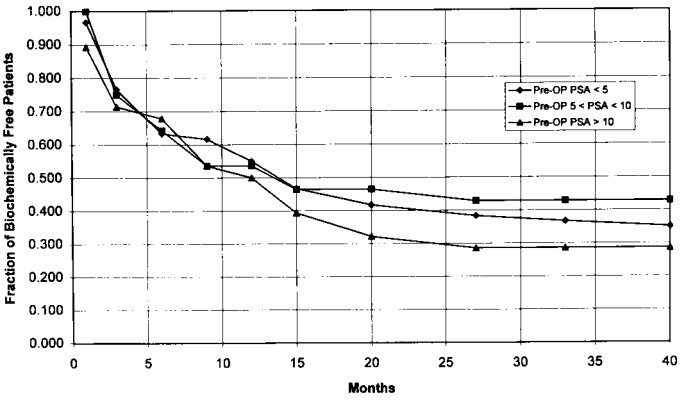

FIG. 5. Kaplan-Meier survival curves for patients with preoperative (*Pre-OP*) PSA less than 5, 5 to 10 and greater than 10 ng./ml. Failure defined as PSA greater than 0.5 ng./ml.

transurethral resection as well as prior radiation, and they were succinctly forewarned that they could virtually be 100% incontinent. Despite such prospects, many of them decided to continue with the procedure, hoping for a cure. Not surprisingly, our results indicated that any patient who underwent prior transurethral procedures is at a much higher risk for incontinence. Otherwise, the postoperative complications from salvage cryoablation are acceptable.

In regard to postoperative results those patients with serum PSA greater than 4 ng./ml. have residual disease and up until our analysis (median followup 18.6 months), 21% of results would be classified as clinical failure. However, there is a discrepancy, as noted previously by Miller et al,[18] between this and the biopsy results, as the majority of those patients with detectable PSA have in fact negative serial postoperative biopsies. The natural conclusion is that these patients have occult distant metastases undetected despite our diligent effort with preoperative metastatic work-up. One could argue that the 4 quadrant and lesion directed biopsies performed in our protocol may have missed minute focal residual disease, especially with the inhomogeneous ultrasonographic appearance and interference from calcifications. However, the majority of these patients have undergone followup re-biopsy, some up to 5 sets, thus decreasing the likelihood of sampling error. The majority of those patients with postoperative PSA between 0.5 and 5.0 ng./ml. have actually remained stable, as supported by the Kaplan-Meier survival curve. Because of the significant percentage of biopsies revealing residual or viable glandular and stromal prostate tissue, it is conceivable that some of these patients have only benign tissue, although the obvious concern is that there is residual viable cancer that has yet to be detected. In support of the notion that this disease may not progress Shinohara et al had noted biochemical and biopsy failure tended to occur within 18 months after treatment.[19]

Followup of the current theories show a proportion of the patients with a sustained PSA of less than 0.5 ng./ml., which is somewhat more favorable than the results reported recently elsewhere.[17] Moreover, median followup duration in this series is somewhat longer at 18.6 months. An obvious criticism of our result is that the patients did not uniformly have an undetectable serum PSA, a target that has been regarded as synonymous with "cure" of prostate cancer. Aside from possible residual viable cancer, the use of a periurethral warming device, although substantially decreasing the incidence of voiding difficulties, undoubtedly has led to preservation of some periurethral prostate tissue. This result is also a source of concern for the persistence of malignancy, although the majority of cancers are located in the peripheral zone rather than the transitional zone. The low incidence of postoperative positive biopsies relative to the number of patients with incidence of viable prostate tissue on biopsies and those with detectable but stable PSA is compatible with this assumption.

From a prostate tissue ablation standpoint, more aggressive maneuvers have been described, including more extensive freezing, insertion of more probes,[20] increasing the number of freeze thaw cycles from 2 and adjunctive transurethral resection.[21] These procedures can result in more extensive cryo-induced morbidity, such as incontinence, fistula formation, and urethral, bladder, neural and muscular damage. We strongly favor a more conservative approach in this select patient group, as our results indicate that acceptable sustained PSA responses can be attained.

Based on our results, the factors that would predict an unfavorable outcome with salvage cryoablation include PSA greater than 10 ng./ml. before cryoablation, a high Gleason

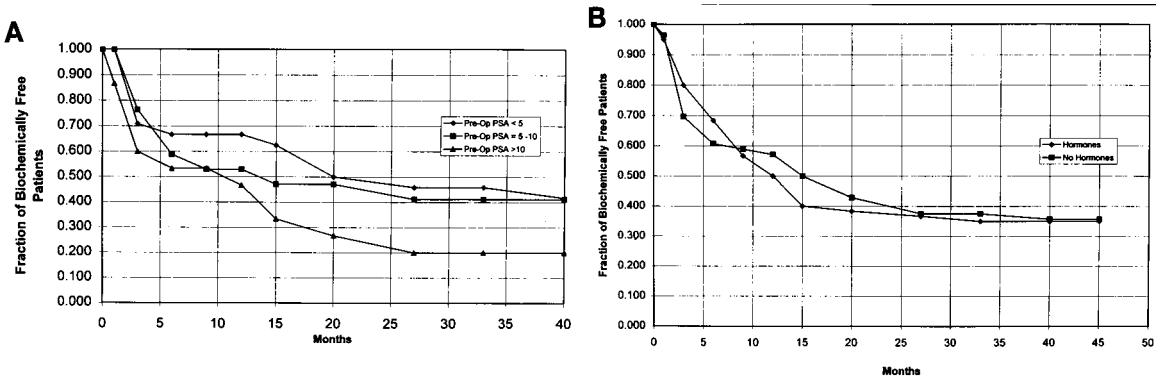

FIG. 6. Kaplan-Meier survival curves. *A*, patients not on cytoreductive hormonal therapy before cryoablation. *B,* patients on and those not on cytoreductive hormonal therapy before cryoablation. Failure defined as PSA greater than 0.5 ng./ml. *Pre-Op*, preoperative.

score before radiotherapy,[8–10] stage T3/T4 disease and likely those patients with increasing PSA despite hormone therapy. This latter patient group probably has systemic disease, which is not curative with any form of local therapy. These findings corroborate those of Pisters et al.[22] The number of positive cores and preoperative prostate volume did not appear to be predictive factors for success, although the data are reflected by extrinsic factors such as neoadjuvant hormone therapy and subjective sampling practices.

In regard to procedure related morbidity we have also identified strong predictive factors for urinary fistula formation, including bulky stage T3B and T4A disease, and incontinence before transurethral resection and repeat urethral instrumentation. The quality of life assessment of salvage cryoablation was reported by Perotte et al as similar to that for salvage radical prostatectomy.[23] Our quality of life assessment indicated favorable patient satisfaction and acceptance of cryoablation.[24]

CONCLUSIONS

In this cohort of patients in whom radiation failed cryoablation has prevented or at least significantly deferred the need for endocrine therapy for some years. More importantly, this result has been achieved with acceptable morbidity. Analysis of our current series has identified predictors of treatment failure and complications, thus facilitating further refinement of the patient selection process. Cryoablation is an acceptable treatment option for those patients in whom radiation has failed, provided vigorous patient selection criteria are adhered to.

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EDITORIAL COMMENT

The article by Chin et al presents important information regarding the selection of patients for salvage cryotherapy after full dose radiation therapy. In this series patients with PSA greater than 10 ng./ml. before salvage cryoablation, clinical stage T3/T4 disease or Gleason score 8 or greater before radiation had significantly higher rates of biochemical recurrence. These findings are consistent with those of our previous study (reference 22 in article). We found that patients with PSA less than 10 ng./ml. before cryoablation and a Gleason score of the recurrent cancer 8 or less had significantly better disease-free survival after salvage cryotherapy. The importance of PSA before cryoablation and the tumor grade has also been shown in patients undergoing salvage prostatectomy. These patients, with preoperative serum PSA greater than 10 ng./ml. (references 6 and 7 in article), and those with high grade cancer[1] have much higher rates of biochemical failure.

Together, these results indicate that the patients most likely to be cured with salvage local therapy are those with PSA less than 10 ng./ml. and Gleason score less than 8 cancer. On the basis of these findings I recommend that young, otherwise healthy, patients who have increasing PSA after radiation therapy be observed closely and undergo biopsy early, while PSA is less than 10 ng./ml., if they wish to consider further aggressive local therapy.

Only 7 patients in this series had positive prostate biopsies after cryotherapy. This study may have underestimated the true rate of local recurrence for several reasons. Of the 118 patients in this series 71 received hormonal therapy before salvage cryotherapy, which may have altered prostate histology and reduced the frequency of positive biopsies. The authors used a 4 quadrant biopsy technique with additional lesion directed biopsies as indicated. Residual disease in patients treated with cryotherapy is often focal,[2] and this biopsy technique may have been associated with significant sampling error. The authors found residual viable normal prostate glands in up to 50% of patients. These data are consistent with our prior study[2] and suggest that it is difficult to completely ablate all prostate tissue with cryotherapy. Because prostate cancer is usually multifocal, and because the frequency of inadequate prostate ablation is up to 50%, as shown by the rate of viable normal glands, I believe that many patients in this series with increasing PSA had inadequate local control and not metastatic disease as the authors suggest.

Finally, which salvage therapy is most likely to cure? I do not think the biochemical results of salvage cryotherapy are nearly as good as those of salvage radical prostatectomy. With a short median followup

of 18.6 months, only 34% of patients in this series were biochemically free of disease with a definition of PSA greater than 0.5 ng./ml., whereas about 65% of those undergoing salvage radical prostatectomy were disease free at 60 months (reference 6 in article),[1] with a definition of PSA greater than 0.2 ng./ml. These apparent differences in biochemical outcome may be related to patient selection, as PSA and tumor grade before cryoablation have profound prognostic significance. Currently, at the M.D. Anderson Cancer Center we are directly comparing biochemical outcome after salvage cryotherapy and at the Mayo Clinic outcome after salvage radical prostatectomy limiting the comparison to patients with PSA less than 10 mg./ml. before cryoablation, Gleason grade 8 or less and no hormonal therapy before or after salvage therapy to minimize bias between the groups. We hope to present our results at the next American Urological Association meeting. Our study may help determine which salvage therapy is most likely to cure.

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REPLY BY AUTHORS

We agree that inadequate local tumor control and sampling error are definite possibilities and a major concern despite repeated negative biopsies. However, we have performed serial biopsies on a large number of these patients beyond 4 years and have encountered only 1 positive biopsy beyond the 2-year mark.

We also agree that biochemical results of salvage cryoablation may be somewhat inferior to those of salvage radical prostatectomy (to our knowledge no randomized series are available). However, we believe that the 2 salvage modalities are suited for somewhat different patient populations. Despite the data indicating similar quality of life outcomes among those undergoing the 2 treatments (reference 23 in article), salvage cryoablation is undoubtedly better tolerated by older patients, especially those with medical co-morbidities. Thus, the 2 modalities are complementary to each other as salvage treatment options for somewhat different patient populations.